806 Biochemical and Hormonal Determinants of Systolic Function

Wednesday, March 27, 1996, 4:00 p.m.–5:00 p.m.
Orange County Convention Center, Room 222

4:00

806-1 Divergent Time Course of Tumor Necrosis Factor-α Induced Impairment of Mechanical Restitution and Depressed Contractility

David R. Murray, Sumanth D. Prabhu, Gregory L. Freeman. *UTHSC and ALMMVH, San Antonio, Texas*

Although *in vitro* studies suggest the negative inotropic effect of TNFα can be attributed to alterations in intracellular calcium (Ca^{++}) homeostasis, the impact of TNFα on sarcoplasmic reticulum SR) function is not known. In the intact heart, SR Ca^{++} release kinetics can be inferred from the mechanical restitution curve (MRC). Accordingly, in 7 autonomically blocked (propranolol 2 mg/kg, atropine 2 mg), conscious dogs instrumented with LV manometers and 3 diameter gauges, we studied MRCs before and after TNFα infusion (40 μg/kg over 1 hour). After priming at a rate of 160 bpm, test pulses were delivered at graded extrasystolic intervals. The mechanical response of the extrasystolic beat was expressed as single beat elastance, normalized to the preceding control beat. Slopes of the end-systolic pressure-volume relation (E_{es}, mmHg/ml) and the time constants (TC, ms) of MR are shown (± SEM):

	Pre-TNFα	1 hr post	4 hr post	7 hr post	24 hr post
E_{es}	5.9 ± 0.5	7.7 ± 0.9†	6.5 ± 0.4	5.3 ± 0.5	4.3 ± 0.9†
TC	57.3 ± 8.2	81.8 ± 5.3	96.7 ± 7.8†	71.7 ± 9.1*	61.7 ± 17.6

*$p < 0.05$, †$p < 0.01$

Conclusion: TNFα affected LV systolic performance in a time dependent biphasic manner. TNFα prolonged MR prior to the development of LV contractile impairment. By 24 hours, TC of the MRC returned to normal despite persistence of marked myodepression. Thus, TNFα induced contractile impairment cannot be solely attributed to abnormalities of SR Ca^{++} release kinetics.

4:15

806-2 Left Atrial Biochemical and Mechanical Changes After Regression of Rapid Pacing Induced Heart Failure: Relation to Left Ventricular Function

Brian D. Hoit, Yanfu Shao, Marjorie Gabel, Darryl Kirkpatrick, Karam Paul, Richard A. Walsh. *University of Cincinnati, Cincinnati, OH*

We recently showed that pacing-induced heart failure (CHF), results in left atrial (LA) hypertrophy, upregulation of the β-myosin heavy chain (MHC) of the LA, increased net atrial work (W_{net}), decreased mean normalized systolic ejection rate (MNSER), and increased LA end systolic elastance (Ees). To determine the mechanical and biochemical changes in LA function that accompany regression (REGRESS) of CHF, 7 dogs were studied 4 weeks after cessation of rapid pacing (250 bpm for 3–4 weeks) and data were compared to those from 7 control dogs (CON) and 10 dogs with CHF. Ees was normalized for LA mass, and W_{net} (calculated as the difference in A and V pressure-volume loop areas), LA ejection fraction (EF) and MNSER corrected for heart rate were compared at a common LA pressure (10 mmHg):

	EF (%)	MNSER (EF/s)	Ees (mmHg/ml/g)	W_{net} (mmHg)
CON (n = 7)	17.4 ± 5.5	1.60 ± 0.44	57 ± 19	0.9 ± 2.4
CHF (n = 10)	13.6 ± 5.1	0.90 ± 0.10*	121 ± 63*	6.9 ± 6.0*
REGRESS (n = 6)	10.2 ± 3.0*	1.25 ± 0.33*†	59 ± 24†	2.5 ± 0.8

*< 0.05 vs. CON, † < 0.05 vs. CHF, ANOVA. Data are mean ± SD.

MHC isoforms from the LA body were separated with SDS-PAGE, stained with anti α and βMHC antibodies, and quantified with laser densitometry. Compared to CON, there was a 40.6% decrease in αMHC and a 77.4% increase in βMHC. LA weight was significantly greater in REGRESS than CON (18.1 ± 3.7 vs. 14.5 ± 1.6 gm). Left ventricular (LV) systolic function and weight were not significantly different in REGRESS, while the time constant of LV relaxation was longer (52.5 ± 4.4 vs 40.8 ± 7.6 ms, $p < 0.05$) and LV end diastolic pressure was greater (12.2 ± 1.8 vs 7.1 ± 2.0 mmHg, $p < 0.05$). We conclude: 1) regression of rapid pacing-induced CHF is associated with normalization of atrial systolic elastance, persistent upregulation of the βMHC isoform and incomplete regression of the LA hypertrophy, and 2) unlike the normalization of left ventricular systolic function observed with cessation of rapid pacing, LA systolic function is persistently abnormal, owing in part, to persistent LV diastolic dysfunction.

4:30

806-3 Myocardial Contractile Protein ATPase Activities and Myosin Heavy-Chain Isoforms in Ovariectomized Rabbits

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Both ovariectomy and long-term estrogen therapy alter myocardial contractility. We compared the effects of ovariectomy, with and without estrogen replacement, on cardiac myofibrillar ATPase activities and myosin heavy-chain (MHC) isoforms. Twenty-four female New Zealand rabbits were ovariectomized and were subsequently treated for one week with either estradiol acetate (0.1 mg/0.1 ml sunflower oil) or sunflower oil. Another twelve rabbits were treated with sunflower oil as a control group. Two weeks of estrogen insufficiency resulted in reduced myofibrillar, Ca^{2+}-activated myosin ATPase activity, but failed to alter actin-activated myosin ATPase activity. Estradiol treatment reversed the decline in enzymatic activity following ovariectomy. Minigel SDS electrophoresis was utilized for separation of individual MHC isoforms. There were no significant changes in MHC isoforms between ovariectomized and control rabbit hearts. However, an additional MHC isoform was identified in estradiol treated hearts. Conclusion: In ovariectomized rabbits estrogen treatment restored Ca^{2+} activated myofibrillar and myosin ATPase activity to control values. An increase in myofibrillar and Ca^{2+} myosin ATPase activities seen in estrogen treated rabbit hearts may be due to the development of a new MHC isoform.

4:45

806-4 Effects of Nitric Oxide Inhalation and L-Arginine Intravenous Infusion on Hemodynamics and Left Ventricular Mechanics in Severe Congestive Heart Failure

Edimar Bocchi, Alvaro Moraes, Antonio Esteves, José Auler-Jr, Maria Carmona, Pedro Graziosi, Giovanni Bellotti, Fulvio Pileggi. *Heart Institute, Sao Paulo University, Brazil*

We investigated the effects of inhaled NO and L-Arginine (L-ar) intravenous (i.v) infusion in 7 pts with CHF, mean age 39 ± 8 years, left ventricular ejection fraction 22 ± 8% (MUGA). We determined at basal condition (B1), during NO inhalation (10 min with 40 p.p.m.) (NO), basal before L-arg infusion (B2) and after L-Arg infusion (500 $mg.kg^{-1}$ in 30 min) the: heart rate (HR) ($b.min^{-1}$), cardiac output (CO) ($l.min^{-1}$), systemic (SVR) and pulmonary vascular resistance (PVR) (Wood units), mean pressures (mmHg) of systemic artery (MSAP), right atrium (RAP), and pulmonary artery wedge (W). The maximal ventricular elastance (E_{max}) ($mmHg.cm^{-1}$) were obtained by simultaneous measurements of LV micromanometer pressures and echo volume.

	HR	MSAP	RAP	W	SVR	PVR	CO	E_{max}
B1	93 ± 17	83 ± 13	7 ± 2	25 ± 9	23 ± 5	2.1 ± 0.6	3.5 ± 0.7	14 ± 2
NO	94 ± 17	86 ± 16	6 ± 2	31 ± 7*	23 ± 6	1.7 ± 0.8	3.6 ± 0.7	15 ± 3
B2	88 ± 15	84 ± 16	7 ± 2	24 ± 8	24 ± 8	2.1 ± 0.6	3.4 ± 0.7	14 ± 4
L-ar	80 ± 16*	70 ± 18*	10 ± 3*	24 ± 6	15 ± 6*	1.9 ± 1.2	4.1 ± 0.8*	13 ± 3

*$p < 0.05$, comparing with respective basal

One pt developed transitory atrioventricular block after L-ar infusion and needed transient pacemaker implantation. NO did not have systemic effects and increased wedge pressure. L-ar appears to have peripheral vasodilator effects in CHF without change in LV mechanics. The L-arginine NO pathway may be involved in mechanisms modulating HR control and conduction in CHF. Pts with CHF may still exhibit ability to vasodilate peripheral vessel by L-arginine NO pathway.

807 Pathophysiology

Wednesday, March 27, 1996, 4:00 p.m.–5:00 p.m.
Orange County Convention Center, Room 314

4:00

807-1 Occult Ischemia During Exercise Is Associated With Increased Cardiovascular Reactivity to Mental Stress in Siblings of Patients With Premature Coronary Disease

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This study was designed to determine whether individuals with occult is-